Estrogen and Progesterone Receptors Expression in Resected Gallbladder from Gall bladder Carcinoma Cases

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Abstract*— *Gallbladder carcinoma is most common malignancy of gartrointestinal tract (GIT) with poor diagnosis. Its prevalence is higher in females that too of northern India. This study aimed to identify the role of sex hormones in carcinoma gallbladder (CA GB). Resected 100 gall bladders of CA GB were examined immune-histo-chemicaly to find out ER and PR status with its association with its underlying histopathology. It was found in this study that PR status was observed in 36% of cases whereas ER status was positive in 2% of CA GB cases. It was also revealed that ER expression was specific and PR expression was more sensitive indicator in differentiating between benign and malignant carcinoma gall bladder.

Keywords*— *Gall Bladder Carcinoma, ER Status, PR Status

1. Introduction

Carcinoma is one of the most common malignancies of the GIT which has a dismal prognosis with a high incidence in North India.[1] Gallstone disease and gallbladder cancers are more frequently observed in females, especially multiparous females.[2,3] Impaired gallbladder emptying during menses & pregnancy and higher prevalence of gallbladder diseases in females with high parity & prolonged fertility depict its association with female sex hormones.[2] Although few of studies showing the presence of estrogen receptor (ER) and progesterone receptor (PR) in benign[4,5] and malignant[6,7] gallbladder lesions but despite of the fact that Gallbladder carcinoma occurs more frequently in women than men, yet expression of the estrogen receptor (ER) and progesterone (PR) have not been much studied.. In the present study an immune-histo-chemical stain was applied to examine the expression of ER and PR status on resected gallbladder carcinomas aimed to study the ER and PR status of gallbladder carcinomas and its association with underlying histopathology.

2. Methodology

A hospital based descriptive type of observational study was carried out on 100 resected gall bladders of gall bladder carcinoma cases in year 2014. All resected gallbladders of gall bladder carcinoma were sent for immune-histo-chemistry in Microbiology and Pathology department. These gall bladders were resected after laparoscopic cholecystectomy for symptomatic gall bladder disease. Resected specimens were immediately fixed in 10% buffered formalin. After gross examination these gall bladders were obtained for processing to prepare paraffin blocks. The processing schedule included dehydration in increasing gradients of alcohol followed by clearing in xylene, and then embedding in paraffin wax. Sections of Paraffin blocks were dewaxed and stained with hematoxylin & eosin stain for the histological diagnosis. These tissues were examined histo-pathologicaly. Tumor differentiation was classified into well, moderately, and poorly differentiated adenocarcinoma depending on the tumor grading.[10] In addition, the presence of other histological variants of carcinoma gallbladder was also noted.

Simultaneously these Paraffin blocks of all 100 gall bladder disease cases were subjected to immunostaining for ER and PR. Immuno-histo-chemistry was performed using automated immuno-stainer using BioGenex Super Sensitive Streptavidin Biotin Detection System Kit with Progesterone Receptor Clone PR 88 and Estrogen Receptor Clone ER 88 antibody. Positivity for ER and PR expression were examined and noted down.

Data thus collected for ER and PR status and histopathology of these resected gall bladders were compiled and analyzed with trial version of SPSS 20. To find out significance of difference in proportion chi-square test was used. For Significance p value equal to or less than 0.05 was considered significant.

3. Results

Present study observed that out of total 100 gall bladder resected 2 (2%) showed ER receptor positivity whereas 36 (36%) showed PR expression positivity. (Fig. 1 & 2)

Figure .1

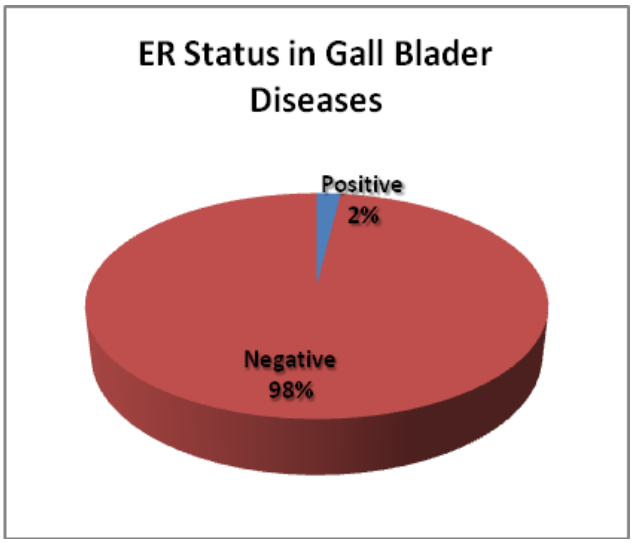
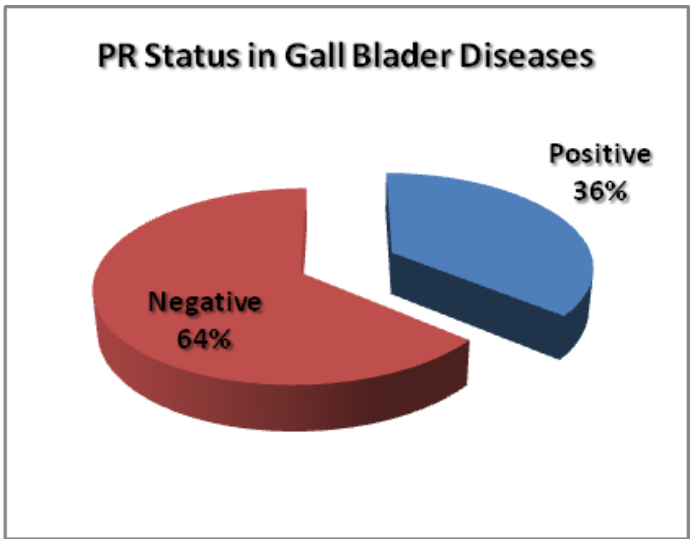


Figure .2



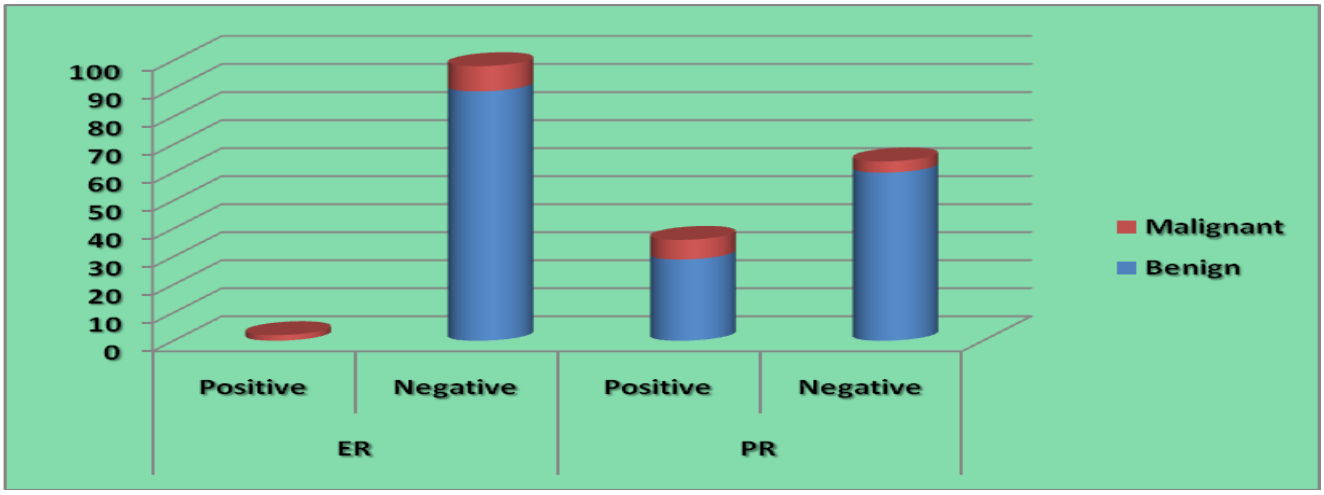
When status of ER and PR status was observed as per benign and malignant carcinoma it was found that it was found to have significant difference ($P<0.05$) where PR had shown more positivity than ER in both type of benign and malignant carcinoma. (Fig. 3)

ER was positive in 2 (18.8%) out of total 11 malignant cases whereas it was found positive in none of benign cases. This variation was found significant ($P<0.05$). Likewise when PR status is conserned it was observed that PR status was positive in 7 (63.63%) out of total 11 malignant cases whereas it was found positive in 29 (34.8%) of cases out of total 89 benign cases. This variation was also found significant ($P<0.05$). (Fig. 3)

When association of ER and PR positivity with age and sex was observed in this study it was found that ER as well as PR status both was not found to be associated with neither age nor sex (Table1)

Association of ER and PR positivity with histo-patholigy of resected gall bladder in this study was observed that although PR status of resected gall bladder was not having significant variation as per underlying pathology but ER status of resected gall bladder was having significant variation as per underlying pathology. ER expression were positive only in adenocarinoma not in other pathologic lesions. (Table 2)

Figure .3



ER status: Chi-square = 8.538 with 1 degrees of freedom; **P Value** = 0.003 **LS=S**

PR status: Chi-square = 2.860 with 1 degrees of freedom; **P Value** = 0.091 **LS=NS**

ER v/s PR Status: Chi-square = 7.239 with 1 degree of freedom; P = 0.007 **LS=S**

Table 1

Association of ER and PR Status with Demographic Variables

Demographic Variables	**Total (N=100)** **No. %**	**ER Positive** **(N=2)**	**PR Positive (N=36)**
Age wise			
31-40	34	0	12
41-50	29	0	10
51-60	21	1	9
61-70	16	1	5
Chi-square Test at 3 DF **P Value LS**		**3.578** **P= 0.419 NS**	**0.622** **P= 0.999 NS**
Sex wise			
Female	85	1	32
Male	15	1	4
Chi-square Test at 1 DF **P Value LS**		**0.160** **P= 0.689 NS**	**0.042** **P= 0.838 NS**

Table 2

Association of ER and PR Status with Gall Bladder Pathology

S. No.	Characteristics of the GB Lesion	Total No. %	ER Positive No. %	PR Positive No. %
1	Acute on Chronic Cholecystitis	3	0	0
2	Acute on Chronic Cholecystitis with Cholelithiasis	3	0	1
3	Adenocarcinoma Gallbladder	8	2	5
4	Cholesterosis	1	0	0
5	Cholesterosis with Cholelithiasis	3	0	1
6	Chronic Cholecystitis	15	0	5
7	Chronic cholecystitis with Cholelithiasis	64	0	22
8	Metastatic Signet Ring Cell Carcinoma	1	0	0
9	Squamous Cell Carcinoma	1	0	1
10	Undifferentiated Carcinoma	1	0	1
11	**Grand Total**	**100**	**2**	**36**
	Chi-square Test at 9 DF **P Value LS**	**8.945** **P= 0.451 NS**	**23.469** **P= 0.005 S**	**8.945** **P= 0.451 NS**

4. Discussion:

Carcinoma of gall bladder is most common malignant lesion of the biliary tract and fifth most common malignancy of the digestive tract. [1, 8] Present study revealed that ER and PR status in resected gall bladders of gall bladder carcinomas were found to be associated with type of carcinoma with more positivity in malignant carcinoma than benign. Other authors had also reported the role of ER and PR expression in their studies[9,10] Former author reported that acting through ER and PR, sex hormones can alter the gallbladder motility by modulating the affinity of receptors in gallbladder to cholecystokinin octapeptide and carbachol.[9] Presence of PR in the gallbladder makes it more susceptible to circulating hormones and their effect on its motility. [10] Alteration in gallbladder motility in association with other predisposing factors may lead to the development of gallstones and malignancy.

Limited studies have shown the presence of ER and PR expression in both normal gallbladder[6] and gallbladder with gallstones. [4,5] Parul Gupta etall[11] had also reported almost similar findings in their observations that although in benign lesion none of the case had shown positivity for any of the two receptors but in malignant cases PR positivity was observed in 52% cases. Parul Guta etall[11] also found significantly higher expression of ER in malignant lesions than in benign lesions (28% vs. 0%). On the contrary, Baskaran et al[6] have shown no such difference. Rather, they found significantly higher expression of PR in malignant lesions (in our study there was no difference).Other author like Ranelletti FO etall[5] and Baskaran V etall[6] reported ER positivity 42% and 20% respectively in benign gallbladder cases with a significant sex difference (more in females than males). In contrast to this in present study none of case has shown ER positivity in benign gallbladder carcinoma. Ranelleti et al[5] studied 50 cases of gallstone disease, and found 82% PR positivity with no significant difference in the expression

between males and females (72.2% vs. 86.2%). In this study also sex wise distribution of positivity of PR was statistically non significant i.e. 37.5% vs. 26.67% in females and males. In contrast to the present study Yamamoto et al[12] have shown significantly higher ER expression in metaplastic lesions, both benign and malignant. Role of the sex hormone in the carcinogenesis of gallbladder cancer is still not clear. Cytoplasmic positivity of ER has ranged from 28.6%[7] to 60%.[13]

When the literarure related to association of ER and PR expression with differentiating type of tumour, studies[12,13,14,15] including the present one, have also showed that poor differentiation is more likely to be associated with low or absent ER expression. In contrast to present studies observations Baskaran et al[6] and Parul Gupta etall[11] however did find significantly higher expression of PR in malignant tissues. Whereas in other studies[11-15] including the present one, that when both ER and PR expression were evaluated, frequency of PR expression was found to be more than ER expression. This may be clinically important in terms of treatment with anti-hormonal therapy, because PR expression is considered as an indicator of a functionally intact receptor system and more accurate indicator of endocrine responsiveness. [16] Similar to ER, association of PR with tumor differentiation is not clear in most of these studies.

In the present study PR expression was not found to be associated with type of gall bladder lesion whereas ER expression was found to be positive only in malignant carcinoma bladder. Other authors like Parul Gupta ellall[11] found PR receptor expression in higher proportion of cases with metaplasia (71%) than without metaplasia (15%). It is well known that chronic inflammation causes epithelial regeneration with adaptive changes (eg, metaplasia) with subsequent development of carcinoma. [17]

CONCLUSIONS

Sex hormones like Estrogen and Progesterone influences gall bladder physiology and have a important role in gall bladder pathology. ER expression is being more specific and PR expression is being more sensitive indicator in malignant gall bladder carcinoma.

REFERENCES

1. Dhir V, Mohandas KM.: Epidemiology of digestive tract cancers in India IV, gallbladder and pancreas.Indian J Gastroenterol 18:24–28, 1999 [PubMed]

2. Chen A, Huminer D.: The role of estrogen receptors in the development of gallstones and gallbladder cancer. Med Hypotheses 36:259–260, 1991 [PubMed]

3. Singletary BK, Van Thiel DH, Eagon PK.: Estrogen and progesterone receptors in human gallbladder.Hepatology 6:574–578, 1986 [PubMed]

4. Daignault PG, Fazekas AG, Rosenthall L, Fried GM.: Relationship between gallbladder contraction and progesterone receptors in patients with gallstones. Am J Surg 155:147–151, 1988 [PubMed]

5. Ranelletti FO, Piantelli M, Farinon AM, Zanella E, Capelli A.: Estrogen and progesterone receptors in the gallbladders from patients with gallstones. Hepatology 14:608–612, 1991 [PubMed]

6. Baskaran V, Vij U, Sahni P, Tandon RK, Nundy S.: Do the progesterone receptors have a role to play in gallbladder cancer? Int J Gastrointest Cancer 35:61–68, 2005 [PubMed]

7. Nakamura S, Muro H, Suzuki S.: Estrogen and progesterone receptors in gallbladder cancer. Jpn J Surg19:189–194, 1989 [PubMed]

8. Carriaga MT, Henson DE.: Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 75(1 Suppl):171–190, 1995 [PubMed]

9. Messa C, Maselli MA, Cavallini A, et al. : Sex steroid hormone receptors and human gallbladder motility in vitro. Digestion 46:214–219, 1990 [PubMed]

10. Hould FS, Fried GM, Fazekas AG, Tremblay S, Mersereau WA.: Progesterone receptors regulate gallbladder motility. J Surg Res 45:505–512, 1988 [PubMed]

11. Parul Gupta, Asha Agrawal, Vishal Gupta, Prem K. Singh, Chyanika Pantola and Sonal Amit. Expression and Clinicopathological significance of Estrogen and progesterone Receptors in Gall bladder Cancer. Gastrointest Cancer Res. 2012 March-Apr; 5(2): 41-47

12. Yamamoto M, Nakajo S, Tahara E.: Immunohistochemical analysis of estrogen receptors in human gallbladder. Acta Pathol Jpn 40:14–21, 1990 [PubMed]

13. Malik IA, Abbas Z, Shamsi Z, et al. : Immuno-histochemical analysis of estrogen receptors on the malignant gallbladder tissue. J Pak Med Assoc 48:123–126, 1998 [PubMed]

14. Park JS, Jung WH, Kim JK, et al. : Estrogen receptor alpha, estrogen receptor beta, and progesterone receptor as possible prognostic factor in radically resected gallbladder carcinoma. J Surg Res 152:104–110, 2009 [PubMed]

15. Sumi K, Matsuyama S, Kitajima Y, Miyazaki K.: Loss of estrogen receptor beta expression at cancer front correlates with tumor progression and poor prognosis of gallbladder cancer. Oncol Rep 12:979–984, 2004 [PubMed]

16. McGuire WL, Horwitz KB, Pearson OH, Segaloff A.: Current status of estrogen and progesterone receptors in breast cancer. Cancer 39(Suppl):2934–2947, 1977 [PubMed]

17. Roa I, de Aretxabala X, Wistuba I.: Histopathology and molecular pathogenesis of gallbladder cancer, in Thomas CR, Fuller CD, editors. (eds): Biliary tract and gallbladder cancer: diagnosis and therapy. New York, Demos Medical Publishing, pp 37–48, 2009